

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

08 December 1999 (08.12.99)

International application No.

PCT/SE99/00319

Applicant's or agent's file reference

R 1923-1 WO

International filing date (day/month/year)

04 March 1999 (04.03.99)

Priority date (day/month/year)

06 March 1998 (06.03.98)

Applicant

RAMACHANDRAN, Janakiraman

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

01 October 1999 (01.10.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

BEST AVAILABLE COPY

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Sean Taylor

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

To:

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

RECEIVED

ENTER 10/04/2000

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 05 April 2000 (05.04.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference R 1923-1 WO	
International application No. PCT/SE99/00319	International filing date (day/month/year) 04 March 1999 (04.03.99)

1. The following indications appeared on record concerning:		
<input checked="" type="checkbox"/> the applicant	<input type="checkbox"/> the inventor	<input type="checkbox"/> the agent
<input type="checkbox"/> the common representative		
Name and Address ASTRA AKTIEBOLAG S-151 85 Södertälje Sweden	State of Nationality SE	State of Residence SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
<input type="checkbox"/> the person	<input checked="" type="checkbox"/> the name	<input type="checkbox"/> the address
<input type="checkbox"/> the nationality		
<input type="checkbox"/> the residence		
Name and Address ASTRAZENECA AB S-151 85 Södertälje Sweden	State of Nationality SE	State of Residence SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary: The change also refers to the name indicated in Box IV of the request form.		
4. A copy of this notification has been sent to:		
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned	
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned	
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:	

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. De Michiel

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

16C3
REC'D 23 JUN 2000

WIPO

PCT

5630

09/284516

Applicant's or agent's file reference R 1923-1 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/SE99/00319	International filing date (day/month/year) [04.03.1998] 04.03.1999	Priority date (day/month/year) [06.03.1999] 06.03.1998
International Patent Classification (IPC) or national classification and IPC ₇ A61K 31/405, A61K 31/445, A61K 31/495, C07D 209/38, C07D 209/34, C07D 401/06		
Applicant [Astra Aktiebolag et al] ASTRAZENECA A.B.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

RECEIVED

JAN 05 2001

TECH CENTER 1600/2900

Date of submission of the demand 01.10.1999	Date of completion of this report 08.06.2000
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Göran Karlsson/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE99/00319

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

- ☒ the international application as originally filed.
- ☐ the description, pages _____, as originally filed,
 pages _____, filed with the demand,
 pages _____, filed with the letter of _____,
 pages _____, filed with the letter of _____.
- ☐ the claims, Nos. _____, as originally filed,
 Nos. _____, as amended under Article 19,
 Nos. _____, filed with the demand,
 Nos. _____, filed with the letter of _____,
 Nos. _____, filed with the letter of _____.
- ☐ the drawings, sheets/fig _____, as originally filed,
 sheets/fig _____, filed with the demand
 sheets/fig _____, filed with the letter of _____,
 sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE99/00319

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11

because:

☒ the said international application, or the said claims Nos. 11

relate to the following subject matter which does not require an international preliminary examination (*specify*):

A method for treatment of the human or animal body by therapy (PCT Rule 67.1(iv)).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

PCT/SE99/00319

1. Statement

Novelty (N)	Claims	1-10	YES
	Claims		NO
Inventive step (IS)	Claims	1-10	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims		NO

The invention relates to the use of certain isatin and oxindole derivatives in the preparation of a medicament for use in the treatment of a mycobacterial disease. The invention also relates to certain isatin and oxindole derivatives containing a phenyl group, a process for their preparation and a pharmaceutical composition comprising these compounds in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Boll. Soc. It. Biol. Sper., Vol. 62, 1986, pp 1449-1455
discloses indol-2,3-dione derivatives having activity against
Mycobacterium paratuberculosis. The compounds according to
the invention differ from these compounds by the R2 group.
Thus there is no information in this document which would lead
a person skilled in the art to use the present compounds in
the manufacture of a medicament for the treatment of a
mycobacterial disease.

Therefore, claims 1-10 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

Indian Journal of Chemistry, Vol. 21B, pp 775-777 and Pharmazie, Vol. 34, 1979, pp 231-232 further disclose the general state of the art which is not considered to be of particular relevance.

28 Rec'd PCT/RO 14 APR 1999

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) R 1923-1 WO

Box No. I TITLE OF INVENTION

NEW USE

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ASTRA AKTIEBOLAG
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

State (that is, country) of nationality:
SE

State (that is, country) of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

RAMACHANDRAN, Janakiraman
Astra Biochemicals Pvt Ltd
P.O. Box 8013
Malleswaram
Bangalore 560 080
India

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
IN

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Intellectual Property, Patents
Astra Aktiebolag
S-151 85 Södertälje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|---|
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |
| <input checked="" type="checkbox"/> LR Liberia | |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐
- ☐
- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

B x No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: * regional Office	international application: receiving Office
item (1) (06.03.1998) 06 March 1998	464/MAS/98	India		
item (2) (20.04.1998) 20 April 1998	9801370-9	Sweden		
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (2)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA)
(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / SE

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

23 October 1998

ITS SE98/00353 Sweden

B x No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 3

description (excluding sequence listing part) : 18

claims : 4

abstract : 1

drawings :

sequence listing part of description :

Total number of sheets : 26

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: GF 4354/98 & 4353/98
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s): (1)
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (specify): ITS SE98/00353

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

B x No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje,  1999



Sten Danielsson
Intellectual Property, Patents, Astra Aktiebolag

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

28 Rec'd PCT/PTO 14 APR 1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL-TYPE SEARCH REPORT

(PCT Article 15.5)

National application No. 9801370-9	Country or Office of filing SE	Applicant's or agent's file reference R 1923-2 SE
Filing date (day/month/year) 20 April 1998		(Earliest) Priority Date (day/month/year)
Applicant Astra Aktiebolag		

Date of request for international-type search 20 April 1998	International-type search request No. SE 98/00353
--	--

This international-type search report has been prepared by this International Searching Authority and is transmitted to the applicant.

This international-type search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (See Box I).

2. ☐ Unity of invention is lacking (See Box II).

3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international-type search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ transcribed by this Authority.

INTERNATIONAL-TYPE SEARCH REPORT

Search request No.

SE 98/00353

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international-type search report has not been established in respect of certain claims for the following reasons:

1. ☒ Claims No.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy,
see rule 39.1.
2. ☐ Claims No.:
because they relate to parts of the national application that do not comply with the prescribed requirements to such an extent that no meaningful international-type search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international-type search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international-type search report covers only those claims for which fees were paid, specifically claims No.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international-type search report is restricted to the invention first mentioned in the claims, it is covered by claims No.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

1
INTERNATIONAL-TYPE SEARCH REPORT

Search request No.

SE 98/00353

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/405, A61K 31/445, A61K 31/495, C07D 209/38, C07D 209/34, C07D 401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Boll. Soc. It. Biol. Sper., Volume 62, No 12, 1986, E. Piscopo et al, "Studies On Heterocyclic Compounds: Indol-2,3-Dione Derivatives. VI. 3-Aryliminoindol-2(3H)-Ones And Their Mannich Bases With Antimicrobial Activity" page 1449 - page 1455 --	1-10
A	Indian Journal of Chemistry, Volume 21B, August 1982, Rajendra S Verma et al, "Synthesis of Alkyl 4-((4'-(1,2-Dihydro-5-chloro-2-oxo-3H-indol-3-ylideneamino)- benzoyl)amino)benzoates & Related Compounds" page 775 - page 777 --	1-10

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international-type search

23 October 1998

Date of mailing of the international-type search report

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Göran Karlsson
Telephone No. +46 8 782 25 00

INTERNATIONAL-TYPE SEARCH REPORT

Search request No.

SE 98/00353

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Pharmazie, Volume 34, No 4, 1979, M. Movrin et al, "Biologisch aktive Azomethine" page 231 - page 232 -- -----	1-10

9/284576

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/405, 31/445, 31/495, C07D 209/38, 209/34, 401/06	A1	(11) International Publication Number: WO 99/44608 (43) International Publication Date: 10 September 1999 (10.09.99)
(21) International Application Number: PCT/SE99/00319 (22) International Filing Date: 4 March 1999 (04.03.99) (30) Priority Data: 464/MAS/98 6 March 1998 (06.03.98) IN 98013270-9 20 April 1998 (20.04.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): RAMACHANDRAN, Janakiraman [US/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NEW USE (57) Abstract The invention provides the use of certain isatin and oxindole derivatives in the preparation of a medicament for use in the treatment of mycobacterial disease.		

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NEW USE

The present invention relates to the use of certain isatin and oxindole derivatives in the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis*, *M. bovis*, *M. avium* and *M. marinum*.

Tuberculosis is still a major public health problem affecting nearly all parts of the world. Based on skin test reactivity it has been estimated that about one-third of the world's population, i.e., 1.7 billion people, are infected with *Mycobacterium tuberculosis*. Despite the availability of effective chemotherapies, it is responsible for three million deaths and from eight to ten million new cases annually and thus remains the leading cause of death world-wide due to a single infectious agent: 26% of all preventable deaths, 7% of all deaths. According to the World Health Organisation, 450,000 deaths per year due to tuberculosis in developing countries occur in children under fifteen years of age, and the disease mostly affects the younger, more productive adults.

There are five front-line drugs known to be highly effective against *M. tuberculosis* and five second-line drugs that can be used when resistance to one or more of the front-line drugs is detected. The preferred mode of treatment for tuberculosis is the short course chemotherapy in which there are two phases. The first phase consists of a daily regimen for two months with isoniazid (300 mg), rifampicin (600 mg), pyrazinamide (3 g) and ethambutol (1.5 g). The second phase or the continuation phase consists of a daily regimen for the next four months with isoniazid and rifampicin. Although infection with drug-sensitive strains of *M. tuberculosis* can be effectively cured with the short course chemotherapy, the cure rate is very poor in most countries due to poor compliance which is reflective of the long duration of therapy.

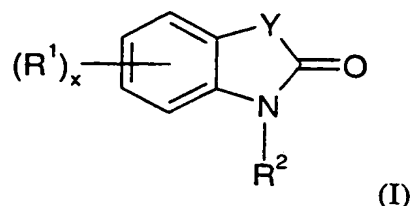
The situation is further complicated by the rapid emergence of multi-drug resistant tuberculosis (MDR-TB) strains. For example, in certain populations, the incidence of resistance to isoniazid is as high as 26% and the resistance to rifampicin is about 15%.

Prior to 1984, about 10% of tubercle bacilli isolated from patients in the United States were resistant to at least one single mycobacterial drug. By 1984, this figure had risen to 52%, of which over half (32%) were resistant to more than one drug (MDR-TB). Ten percent of the recorded MDR-TB cases have occurred in previously healthy people whose mortality rate - 70 to 90% - has been nearly the same as that of immunosuppressed individuals with MDR-TB. The number of cases of MDR-TB has doubled since 1984 and in many of them the tubercle bacilli are resistant to both isoniazid and rifampicin. The median interval between diagnosis of MDR-TB and death is only four weeks and therefore MDR-TB demands a shorter response time between diagnosis and appropriate commencement of treatment. However, MDR-TB is difficult to treat as such since most patients do not respond very well to the second-line drugs and the cost of alternate treatment procedures, including hospitalisation and possibly surgery, increases the cost to as much as ten times the cost of traditional treatment.

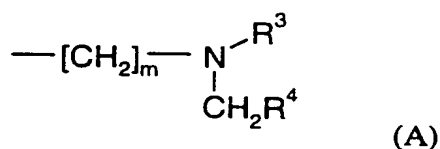
Thus, there is an urgent medical need to identify new drugs with significant therapeutic activity against single- or multiple-drug resistant strains of *M. tuberculosis* and with pharmacokinetic properties that permit reduced dosing which will in turn encourage better compliance.

WO 93/12085 and WO 94/29272 describe two classes of isatin and oxindole derivatives which function as acetylcholinesterase inhibitors and which have application as pharmaceuticals in the treatment of cognitive dysfunctions such as Alzheimer's disease, senile dementia, Parkinson's disease, Down's syndrome and Huntington's chorea.

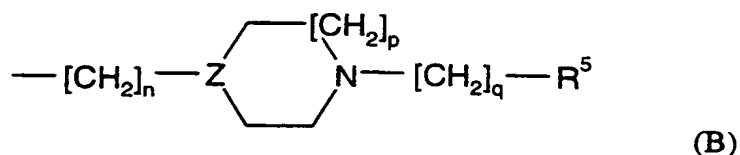
In accordance with the present invention, there is provided the use of a compound of general formula



wherein x represents 0 or 1, R¹ represents a 3- to 7-membered (hetero)cycloalkyl group or a phenyl group, Y represents a group CH₂ or >C=O, and R² represents either a C₁-C₁₂ alkyl group optionally substituted by one or more halogen atoms,
a group



wherein m represents an integer from 3 to 7, R³ represents a C₁-C₆ alkyl group and R⁴ represents a cyclohexyl or phenyl group optionally substituted by one or more substituents selected from the group consisting of a halogen atom, C₁-C₆ alkyl and C₁-C₆ alkoxy group,
or a group



wherein n represents an integer from 2 to 4, p and q independently represent an integer from 1 to 2, Z represents N or CH and R⁵ represents a cyclohexyl or phenyl group optionally substituted by one or more substituents selected from the group consisting of a halogen atom, C₁-C₆ alkyl and C₁-C₆ alkoxy group,
or a pharmaceutically-acceptable salt or solvate thereof in the manufacture of a
medicament for use in the treatment of a mycobacterial disease, in particular tuberculosis.

Preferably Y in formula (I) represents a group >C=O.

Preferably R^1 represents a 5- to 7-membered (hetero)cycloalkyl group (e.g. a cyclopentyl, cyclohexyl, cycloheptyl, pyrrolidinyl, imidazolinyl, pyrazolidinyl, piperidinyl, piperazinyl or morpholinyl group) or a phenyl group. Most preferably R^1 represents a cyclopentyl, cyclohexyl, cycloheptyl or 1-piperidinyl group. Particularly advantageous compounds of formula (I) to use are those in which the group R^1 is located in the 5- or 7-position of the bicyclic ring system.

R^2 represents either a C_1 - C_{12} , preferably C_4 - C_{12} , alkyl group (e.g. a methyl, ethyl, propyl, butyl, 2-methylpropyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl or dodecyl group); a group (A) as defined above in which m represents an integer from 3 to 7, preferably 4 or 5, R^3 represents a C_1 - C_6 alkyl group (e.g. a methyl, propyl, butyl, pentyl, hexyl or especially ethyl group) and R^4 represents a cyclohexyl or, preferably, phenyl group optionally substituted by one or more, e.g. one, two, three or four, substituents selected from the group consisting of a halogen atom (e.g. fluorine, chlorine or bromine), C_1 - C_6 alkyl (e.g. methyl, ethyl or propyl) and C_1 - C_6 alkoxy (e.g. methoxy, ethoxy or propoxy) group; or a group (B) as defined above in which n represents an integer from 2 to 4, preferably 2, p and q independently represent an integer of 2 or preferably 1, Z represents N or CH and R^5 represents a cyclohexyl or, preferably, phenyl group optionally substituted by one or more, e.g. one, two, three or four, substituents selected from the group consisting of a halogen atom (e.g. fluorine, chlorine or bromine), C_1 - C_6 alkyl (e.g. methyl, ethyl or propyl) and C_1 - C_6 alkoxy (e.g. methoxy, ethoxy or propoxy) group.

In the present invention, it is preferred to use a compound being:

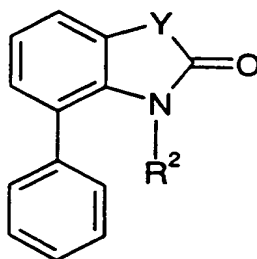
- 5-Cyclohexyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1H-indole-2,3-dione;
- 7-Cycloheptyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
- 5-Cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione;
- 5-Cyclohexyl-1,3-dihydro-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2H-indol-2-one;
- 1-(4-(N-Ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione;
- 5-Phenyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
- 7-Cyclopentyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;

- 5-(1-Piperidiny)-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
1-(4-Bromobutyl)-5-cyclohexyl-1H-indole-2,3-dione;
1-Nonyl-7-phenyl-1H-indole-2,3-dione;
1-Heptyl-7-phenyl-1H-indole-2,3-dione;
5 1-Octyl-7-phenyl-1H-indole-2,3-dione;
1-Decyl-7-phenyl-1H-indole-2,3-dione;
1-Undecyl-7-phenyl-1H-indole-2,3-dione;
1-Pentyl-7-phenyl-1H-indole-2,3-dione;
1-Butyl-7-phenyl-1H-indole-2,3-dione;
10 1-(2-Methylpropyl)-7-phenyl-1H-indole-2,3-dione;
1-Hexyl-7-phenyl-1H-indole-2,3-dione;
1-Dodecyl-7-phenyl-1H-indole-2,3-dione; or
1-(4-Bromobutyl)-7-phenyl-1H-indole-2,3-dione;
or a pharmaceutically-acceptable salt or solvate thereof.

15

The compounds of formula I may be prepared by processes known in the art or by processes analogous to those known in the art, for example, as described in WO 93/12085 and WO 94/29272.

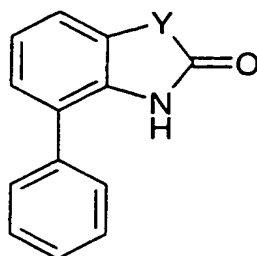
- 20 Some of the compounds of formula (I) above are novel. Therefore, the present invention further provides a compound of the general formula



(I')

- wherein Y and R² are as hereinbefore defined, or a pharmaceutically-acceptable salt or
25 solvate thereof.

The present invention still further provides a process for preparing a compound of formula (I') which comprises reacting a compound of formula



(II)

5 in which Y is as hereinbefore defined, with a compound of general formula (III), R^2-L , where L represents a leaving group such as a halogen atom and R^2 is as hereinbefore defined, and optionally thereafter forming a pharmaceutically-acceptable salt or solvate thereof.

10 The process may conveniently be carried out in a solvent such as dimethylformamide or tetrahydrofuran and in the presence of a base such as triethylamine, anhydrous potassium carbonate or sodium hydride. The process will suitably be carried out at a temperature in the range from 0 to 100 °C.

15 It will be appreciated by those skilled in the art that in the process of the present invention certain functional groups in the intermediate compounds may need to be protected by protecting groups. Thus, the final stage in the preparation of the compounds of formula (I') may involve the removal of one or more protecting groups.

20 The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

25 The compounds of formula (I) or (I') may be converted to a pharmaceutically-acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride,

hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

5 Certain compounds of formula (I) or (I') are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) or (I') and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

10 The compounds according to the present invention are advantageous in that they possess bactericidal activity against mycobacteria, particularly pathogenic mycobacteria such as *Mycobacterium tuberculosis*, *M. bovis*, *M. avium* and *M. marinum*. Accordingly, in another aspect, the invention provides a method of treating a patient suffering from, or at risk of, a mycobacterial disease, which comprises administering to the
15 patient a therapeutically effective amount of a compound of formula (I) or (I'), or a pharmaceutically-acceptable salt or solvate thereof, as defined above.

 The compounds of formula (I) or (I') and pharmaceutically-acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of
20 a pharmaceutical composition in which the formula (I) or (I') compound/salt/solvate (active ingredient) is in association with a pharmaceutically-acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a
25 pharmaceutically-acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition. The pharmaceutical composition may additionally contain another anti-tubercular agent and/or various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I'), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I'), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically-acceptable adjuvant, diluent or carrier.

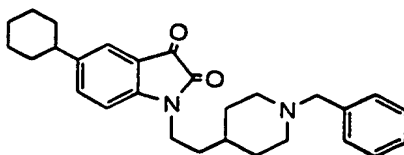
The daily dosage of formula (I) or (I') compound administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the mycobacterial disease indicated. However, in general, satisfactory results will be obtained when the compound of formula (I) or (I') is administered at a daily dosage not exceeding 1 g, e.g. in the range from 10 to 50 mg/kg body weight.

The compounds according to the invention may be administered systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions.

The present invention will be further illustrated with reference to the following examples.

Example 1

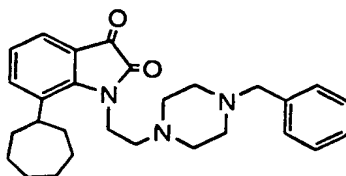
5-Cyclohexyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1H-indole-2,3-dione



The title compound was prepared as described in Example 104 of WO 93/12085.

Example 2

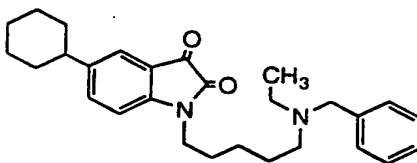
7-Cycloheptyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione



5 The title compound was prepared as described in Example 63 of WO 93/12085.

Example 3

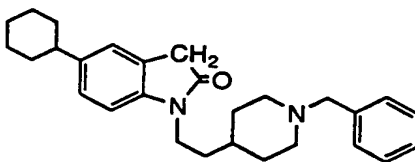
5-Cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione



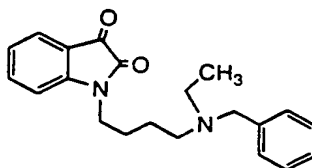
The title compound was prepared as described in Example 22 of WO 94/29272.

Example 4

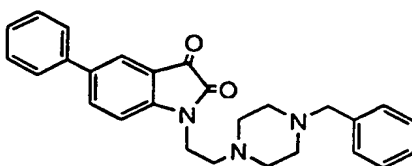
5-Cyclohexyl-1,3-dihydro-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2H-indol-2-one



The title compound was prepared as described in Example 107 of WO 93/12085.

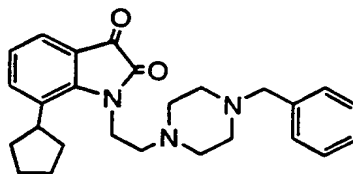
Example 5**1-(4-(N-Ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione**

5 The title compound was prepared as described in Example 19 of WO 94/29272.

Example 6**5-Phenyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione**

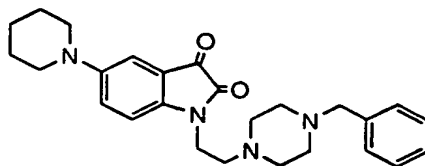
10

The title compound was prepared as described in Example 97 of WO 93/12085.

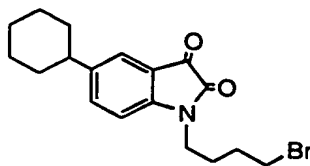
Example 7**7-Cyclopentyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione**

15

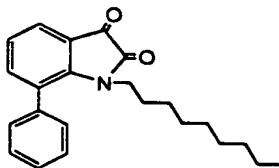
The title compound was prepared as described in Example 61 of WO 93/12085.

Example 8**5-(1-Piperidinyl)-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione**

5 The title compound was prepared in a manner analogous to Example 14 of WO 93/12085 but using 5-(1-piperidinyl)-1H-indole-2,3-dione.

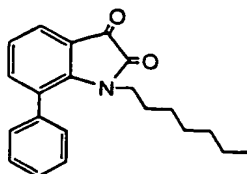
Example 9**1-(4-Bromobutyl)-5-cyclohexyl-1H-indole-2,3-dione**

10 The title compound was prepared as described in Example 29 of WO 94/29272.

Example 10**1-Nonyl-7-phenyl-1H-indole-2,3-dione**

15 The title compound was prepared in a manner similar to the process step described in the text from Page 7, line 34 to Page 8, line 5 of WO 94/29272 but using a haloalkane such as 1-bromononane together with 7-phenyl-1H-indole-2,3-dione.

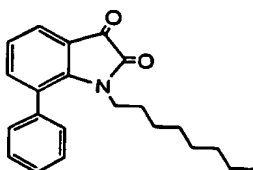
20 ¹H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.9-1.3 (12H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 11**1-Heptyl-7-phenyl-1H-indole-2,3-dione**

5 The title compound was prepared as described in Example 10 above except that 1-bromoheptane was used.

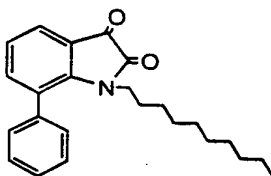
^1H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.9-1.3 (8H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

10 **Example 12**

1-Octyl-7-phenyl-1H-indole-2,3-dione

15 The title compound was prepared as described in Example 10 above except that 1-bromooctane was used.

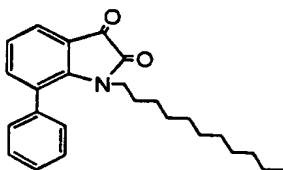
^1H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.9-1.3 (10H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 13**1-Decyl-7-phenyl-1H-indole-2,3-dione**

5 The title compound was prepared as described in Example 10 above except that 1-bromodecane was used.

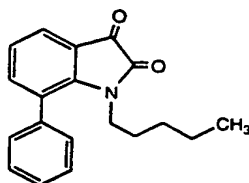
^1H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.9-1.3 (14H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

10 **Example 14**

1-Undecyl-7-phenyl-1H-indole-2,3-dione

15 The title compound was prepared as described in Example 10 above except that 1-bromoundecane was used.

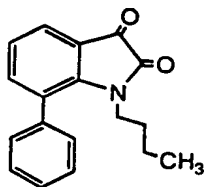
^1H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.8-1.3 (16H, m), 3.3 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 15**1-Pentyl-7-phenyl-1H-indole-2,3-dione**

5 The title compound was prepared as described in Example 10 above except that 1-bromopentane was used.

^1H NMR : δ 0.6-0.8 (5H, m), 0.9-1.1 (2H, m), 1.1-1.3 (2H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

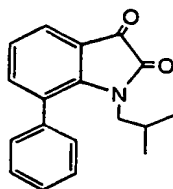
10 **Example 16**

1-Butyl-7-phenyl-1H-indole-2,3-dione

The title compound was prepared as described in Example 10 above except that

15 1-bromobutane was used.

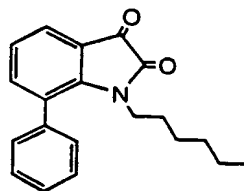
^1H NMR : δ 0.6 (3H, t), 0.7-0.8 (2H, m), 1.1-1.3 (2H, m), 3.3 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 17**1-(2-Methylpropyl)-7-phenyl-1H-indole-2,3-dione**

5 The title compound was prepared as described in Example 10 above except that 1-bromo-2-methylpropane was used.

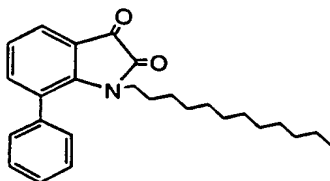
^1H NMR : δ 0.5 (6H, d), 1.3-1.5 (1H, m), 3.2 (2H, d), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

10 **Example 18**

1-Hexyl-7-phenyl-1H-indole-2,3-dione

15 The title compound was prepared as described in Example 10 above except that 1-bromohexane was used.

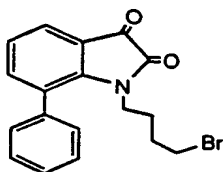
^1H NMR : δ 0.6-0.7 (2H, m), 0.7 (3H, t), 0.8-1.0 (2H, m), 1.0-1.2 (4H, m), 3.3 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 19**1-Dodecyl-7-phenyl-1H-indole-2,3-dione**

5 The title compound was prepared as described in Example 10 above except that 1-bromododecane was used.

^1H NMR : δ 0.6-0.7 (2H, m), 0.85 (3H, t), 0.9-1.4 (18H, m), 3.3 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

10 **Example 20**

1-(4-Bromobutyl)-7-phenyl-1H-indole-2,3-dione

15 The title compound was prepared according to the process step described in the text from Page 7, line 34 to Page 8, line 5 of WO 94/29272 using 7-phenyl-1H-indole-2,3-dione and 1,4-dibromobutane.

^1H NMR : δ 0.7-0.8 (2H, m), 1.1-1.3 (4H, m), 1.6-1.8 (2H, m), 3.2-3.4 (4H, m), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 21

Each of the compounds of Examples 1 to 20 was assessed for bactericidal activity against *M. tuberculosis* by measuring its minimum inhibitory concentration (MIC) in the "BACTEC" (trade mark) system developed by Becton-Dickinson Diagnostic Instrument Systems, Sparks, U.S.A., which is based on a radiometric principle whereby carbon dioxide released by the catabolism of ^{14}C -palmitate is spectrophotometrically detected and quantitated in arbitrary units of measurement referred to as growth index (GI) units.

Thus, "BACTEC" vials were inoculated with 0.1 ml of *M. tuberculosis* (final bacterial concentration, 1×10^5 colony forming units per ml) and 0.1 ml of test compound in a range of concentrations. GI values were monitored until a value of ≥ 30 was achieved for the 1:100 dilution control.

For the purpose of this test, MIC is defined as the minimum concentration of test compound that effects a >95% inhibition of the culture in comparison to the undiluted control, when the control reaches a GI value of 999.

Endpoint determination (>99% inhibition) is based on a conventional 1% resistance cut-off, wherein the organism is considered resistant to a particular concentration of test compound if growth of greater than 1% of the bacterial population is observed. Thus, a comparison is made between growth of the organism in the presence of a pre-determined concentration of test compound and growth of the same organism diluted 1:100 in the absence of any test compound. The change in the GI values (ΔGI) is used to determine the endpoint susceptibility of the organism to the test compound. If the ΔGI of the 1:100 control is greater than the ΔGI in the presence of the test compound, then the concentration of test compound used is considered to be bactericidal (>99% inhibition) for the organism.

The MIC of the compounds of Examples 1 to 20 were determined for the following strains of *M. tuberculosis*:

H37Rv,

H37Ra,

5 1 clinical isolate susceptible to isoniazid, rifampicin, ethambutol and streptomycin [E:22/95; Estonia],

1 clinical isolate resistant to isoniazid [H:997/94; Honduras], 1 clinical isolate resistant to isoniazid and ethambutol [E:5/94; Estonia],

1 clinical isolate resistant to isoniazid and rifampicin [H:44/95; Honduras],

10 1 clinical isolate resistant to isoniazid and streptomycin [S:150/96; Sweden],

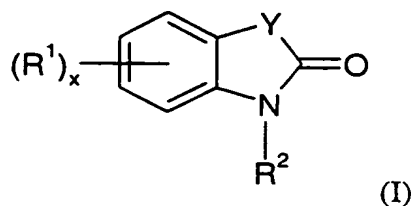
1 clinical isolate resistant to isoniazid, rifampicin and streptomycin [AA:063; Ethiopia],

3 clinical isolates resistant to isoniazid, rifampicin, streptomycin and ethambutol [P:24/95; Estonia, S:39/95; Nepal, S:42/95; China, H:1005/94; Honduras],

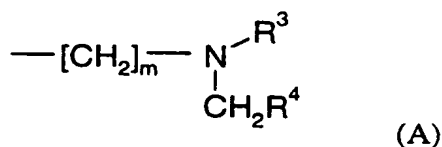
15 and were found in all cases to be less than or equal to 20 µg/ml. Therefore, the compounds of Examples 1 to 20 demonstrate effective bactericidal activity against the above strains of *M. tuberculosis* which include single- and multiple-drug resistant strains.

CLAIMS

1. Use of a compound of general formula

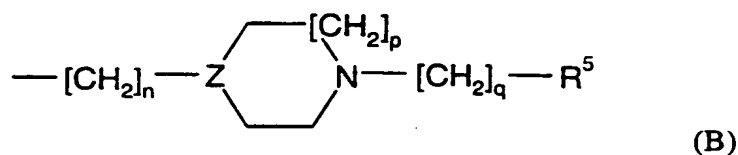


5 wherein x represents 0 or 1, R¹ represents a 3- to 7-membered (hetero)cycloalkyl group or a phenyl group, Y represents a group CH₂ or >C=O, and R² represents either a C₁-C₁₂ alkyl group optionally substituted by one or more halogen atoms, a group



10 wherein m represents an integer from 3 to 7, R³ represents a C₁-C₆ alkyl group and R⁴ represents a cyclohexyl or phenyl group optionally substituted by one or more substituents selected from the group consisting of a halogen atom, C₁-C₆ alkyl and C₁-C₆ alkoxy group,

or a group



15 wherein n represents an integer from 2 to 4, p and q independently represent an integer from 1 to 2, Z represents N or CH and R⁵ represents a cyclohexyl or phenyl group optionally substituted by one or more substituents selected from the group consisting of a halogen atom, C₁-C₆ alkyl and C₁-C₆ alkoxy group,

20 or a pharmaceutically-acceptable salt or solvate thereof in the manufacture of a medicament for use in the treatment of a mycobacterial disease.

2. Use according to claim 1, wherein the mycobacterial disease is tuberculosis.

3. Use according to claim 1 or claim 2, wherein Y represents a group $>C=O$.
4. Use according to any one of claims 1 to 3, wherein R^1 represents a 5- to 7-membered (hetero)cycloalkyl group or a phenyl group.
5. Use according to claim 4, wherein R^1 is located in the 5- or 7-position.
6. Use according to any one of the preceding claims, wherein R^2 represents either a C_4 - C_{12} alkyl group, a group (A) in which R^4 represents a phenyl group and m and R^3 are as defined in claim 1, or a group (B) in which n is 2, p is 1, q is 1, Z is N or CH and R^5 represents a phenyl group.
7. Use of a compound being:
- 5-Cyclohexyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1H-indole-2,3-dione;
- 7-Cycloheptyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
- 5-Cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione;
- 5-Cyclohexyl-1,3-dihydro-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2H-indol-2-one;
- 1-(4-(N-Ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione;
- 5-Phenyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
- 7-Cyclopentyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
- 5-(1-Piperidinyl)-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
- 1-(4-Bromobutyl)-5-cyclohexyl-1H-indole-2,3-dione;
- 1-Nonyl-7-phenyl-1H-indole-2,3-dione;
- 1-Heptyl-7-phenyl-1H-indole-2,3-dione;
- 1-Octyl-7-phenyl-1H-indole-2,3-dione;
- 1-Decyl-7-phenyl-1H-indole-2,3-dione;
- 1-Undecyl-7-phenyl-1H-indole-2,3-dione;
- 1-Pentyl-7-phenyl-1H-indole-2,3-dione;
- 1-Butyl-7-phenyl-1H-indole-2,3-dione;
- 1-(2-Methylpropyl)-7-phenyl-1H-indole-2,3-dione;

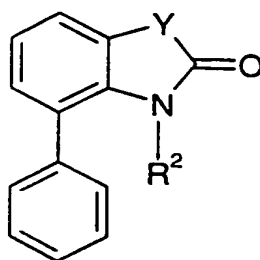
1-Hexyl-7-phenyl-1H-indole-2,3-dione;

1-Dodecyl-7-phenyl-1H-indole-2,3-dione; or

1-(4-Bromobutyl)-7-phenyl-1H-indole-2,3-dione;

or a pharmaceutically-acceptable salt or solvate thereof in the manufacture of a
5 medicament for use in the treatment of a mycobacterial disease.

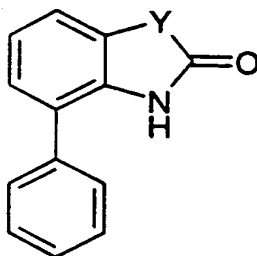
8. A compound of the general formula



(I')

10 wherein Y and R² are as defined in claim 1, or a pharmaceutically-acceptable salt or solvate thereof.

9. Process for the preparation of a compound of formula (I') as claimed in claim 8, which comprises reacting a compound of formula



(II)

15 in which Y is as defined in claim 1, with a compound of general formula (III), R²-L, where L represents a leaving group and R² is as defined in claim 1, and optionally thereafter forming a pharmaceutically-acceptable salt or solvate thereof.

10. A pharmaceutical composition comprising a compound of formula (I'), or a pharmaceutically-acceptable salt or solvate thereof, as defined in claim 8 in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

- 5 11. A method of treating a patient suffering from, or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as defined in any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00319

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/405, A61K 31/445, A61K 31/495, C07D 209/38, C07D 209/34,
C07D 401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Boll. Soc. It. Biol. Sper., Volume 62, No 12, 1986, E. Piscopo et al, "Studies On Heterocyclic Compounds: Indol-2,3-Dione Derivatives. VI. 3-Aryliminoindol-2(3H)-Ones And Their Mannich Bases With Antimicrobial Activity" page 1449 - page 1455 --	1-10
A	Indian Journal of Chemistry, Volume 21B, August 1982, Rajendra S Verma et al, "Synthesis of Alkyl 4-((4'-(1,2-Dihydro-5-chloro-2-oxo-3H-indol-3- -ylideneamino)- benzoyl)amino)benzoates & Related Compounds" page 775 - page 777 --	1-10
A	Pharmazie, Volume 34, No 4, 1979, M. Movrin et al, "Biologisch aktive Azomethine" page 231 - page 232 --	1-10

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28 April 1999

Date of mailing of the international search report

10 -06- 1999

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00319

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.